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LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER

STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/667,569

Examiner

David J. Steadman

Applicant(s)

YOCUM ET AL.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 February 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,7,12,14-34,36,37,39-44 and 46-51 is/are pending in the application.
- 4a) Of the above claim(s) 14-18,20-23,25,29-32,36,37,39-44,46-48 and 50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,7,12,19,24,26-28,33,34,49 and 51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

Application Status

- [1]** Claims 1, 2, 7, 12, 14-34, 36, 37, 39-44, 46-51 are pending in the application.
- [2]** Applicants' election with traverse of Group XIV, claims 41, 42, 46, 47, and 49-51 in Paper No. 14, filed 02/05/03, is acknowledged.
- [3]** Applicants' cancellation of claims 35, 38, 52, 53, 62, 67-75, 82, 83, 88, 90, 97, 99, 102, 104, 106, and 108-110 in Paper No. 14 is acknowledged.

Election/Restrictions

- [4]** Applicants traverse the restriction requirement by arguing that the examiner has improperly restricted the claims into Groups I-XXII and that the claims should instead be restricted to a smaller number of generic inventions including patentably distinct inventions as set forth in the initial restriction requirement of Paper No. 7. In a telephone conversation with Ms. Debra J. Milasincic on 02/27/03, the examiner indicated that, upon reconsideration of the restriction requirement, the claims would be restricted instead according to the restriction as set forth in Paper No. 7. Applicants agreed to that the claims would be restricted according the restriction of Paper No. 7, wherein applicants elected Group I, claims 1, 2, 7, 12, 14-34, 36, 37, 39-44, and 46-51 and species d), drawn to a method of producing a panto-compound by culturing a microorganism overexpressing ketopantoate reductase (panE). This election was made without traverse. In Paper No. 10, applicants indicated that the claims readable on the elected species are as follows: 1, 2, 7, 12, 19, 24, 26-28, 33, 34, 48, 49, and 51 (see page 4 of Paper No. 10). It is noted that claim 48 is not drawn to the elected species and was not included in the claim groupings for the species of Group d) in the restriction of Paper No.7. Therefore, claim 48 has been withdrawn from consideration. Thus, claims 1, 2, 7, 12, 19, 24, 26-28, 33, 34, 49, and 51 have been examined to the extent the claims read on the elected species, i.e., ketopantoate reductase (panE).

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[5] Claims 14-18, 20-23, 25, 29-32, 36, 37, 39-44, 46-48, and 50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Information Disclosure Statement

[6] The information disclosure statement (IDS) filed 07/25/02 as Paper No. 12 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. It is noted that none of the references cited in the IDS has been filed with the instant application. The examiner has made an earnest attempt to locate the cited references without success. In order to ensure delivery of the references to the examiner, it is suggested that applicants have the references hand delivered to the receptionist of Group 1600 and contact the examiner upon delivery.

Specification/Informalities

[7] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Method of Producing a Panto-Compound Using a Microorganism Overexpressing a Pantothenate Biosynthetic Enzyme". See MPEP § 606.01.

Claim Objections

[8] Claim 24 is objected to as depending upon non-elected claim 14. For purposes of examination, claim 24 has been examined as though the claim depends only from claim 19.

[9] Claim 49 is objected to as being dependent upon a non-elected claim. For purposes of examination, the claim has been elected as though the limitations of claims 39 and 41 were incorporated into the claim.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[10] Claims 19, 24, 26, 27, 33, 34, and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- a. Claims 1 (claim 2 dependent therefrom), 7 (claim 12 dependent therefrom), and 51 are unclear in the recitation of "panto-compound". The specification defines the term as "pantothenate and other key compounds of the pantothenate biosynthetic pathway" at page 12, lines 3 and 4. While Figure 1 shows a pantothenate biosynthetic pathway and intermediates thereof, there is no indication in the specification, claims, or figures as to those compounds of the pantothenate biosynthetic pathway that are considered to be "key compounds" and thus, the scope of panto-compounds produced by the claimed methods is unclear.
- b. The term "significantly high yield" in claim 19 (claims 24, 26, 27, 33, and 34 dependent therefrom) is a relative term which renders the claim indefinite. The term "significantly high yield" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claim should define and clearly state as to what the level of pantothenate is being compared by, for example, inserting "as compared to an unmanipulated microorganism" or "as compared to a wild-type microorganism" at the end of the claim.
- c. Claims 27, 34, and 49 are unclear in the recitation of "panE1 nucleic acid sequence" and "panE". The specification defines "panE" at page 39, however, the scope of nucleic acids encompassed by the terms remains unclear. For purposes of examination, the examiner has interpreted the term "panE1" and "panE" as a nucleic acid encoding a polypeptide having

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ketopantoate reductase enzymatic activity. It is suggested that applicants clarify the meaning of the terms "panE1" and "panE".

d. Claim 49 is unclear in the recitation of "coaX". The specification defines "coaX" at pages 40-42, however, the scope of nucleic acids encompassed by the term remains unclear. For purposes of examination, the examiner has interpreted the term "coaX" as a nucleic acid encoding a polypeptide having pantothenate kinase enzymatic activity. It is suggested that applicants clarify the meaning of the term "coaX".

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[11] Claims 1, 2, 7, 12, 19, 24, 26-28, 33, 34, 49, and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 2 are drawn to a method of producing a panto-compound by culturing a microorganism overexpressing a genus of *Bacillus* (claim 1) or *Bacillus subtilis* (claim 2) pantothenate biosynthetic enzymes having any structure. Claims 7 and 12 are drawn to a method of producing a panto-compound by culturing a genus of ketopantoate reductase-overexpressing (KPAR-O) microorganisms (claim 7) and optionally wherein microorganism further overexpresses another pantothenate biosynthetic enzyme (claim 12). Claims 19 (claim 28 dependent therefrom), 24, 26, 27, and 33 are drawn to a beta-alanine independent high yield production method of producing pantothenate by culturing a genus of manipulated microorganisms (claim 19), and optionally wherein the microorganism has a deregulated pantothenate biosynthetic pathway (claim 24), and optionally wherein the

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microorganism overexpresses ketopantoate reductase (claim 33), or optionally wherein the microorganism overexpresses ketopantoate reductase (claim 26) or is transformed with a vector comprising a panE nucleic acid sequence (claim 27) or a *B. subtilis* panE nucleic acid sequence (claim 34). Claim 49 is drawn to a method for enhancing production of a panto-compound comprising culturing a microorganism having a genus of mutant pantothenate kinases and overexpressing a genus of panE genes. Claim 51 is drawn to a method for enhancing production of a panto-compound comprising culturing a genus of microorganisms having a deregulated pantothenate biosynthetic pathway and has a genus of mutations that result in reduced pantothenate kinase activity such that panto-compound production is enhanced.

Regarding claims 1 and 2, the specification teaches only a single representative species of the genus of recited microorganisms overexpressing a *Bacillus* or *Bacillus subtilis* pantothenate biosynthetic enzymes, i.e., a microorganism transformed with an expression vector comprising the nucleic acid of SEQ ID NO:29 encoding the ketopantoate reductase of SEQ ID NO:30. Regarding claims 7 and 12, the specification teaches only a single representative species of the genus of recited ketopantoate reductase-overexpressing microorganisms, i.e., a microorganism transformed with an expression vector comprising a nucleic acid encoding a ketopantoate reductase. Regarding claims 19, 24, and 26-28, the specification discloses only a single representative species of the genus of recited manipulated microorganisms optionally with a deregulated pantothenate biosynthetic pathway, i.e., a microorganism transformed with an expression vector comprising a nucleic acid encoding a ketopantoate reductase. Regarding claims 33 and 34, the specification teaches only a single representative species of the genus of recited manipulated microorganisms further having a deregulated pantothenate biosynthetic pathway overexpressing *Bacillus* ketopantoate reductase or panE1, i.e., a microorganism transformed with an expression vector comprising the nucleic acid of SEQ ID NO:29 encoding the ketopantoate reductase of SEQ ID NO:30. Regarding claims 49 and 51, the specification teaches only a single representative species of the genus of recited microorganisms having a mutant coaX or pantothenate kinase and co-expressing panE, i.e., a microorganism with a deletion of the coaX of SEQ ID NO:9 and transformed with an expression vector

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comprising a nucleic acid encoding a ketopantothenate reductase or a microorganism transformed with an expression vector comprising a nucleic acid encoding an S176L mutation in the *coaA* gene product of SEQ ID NO:2 or a Y181H mutation in the *coaA* gene product of SEQ ID NO:3 and co-transformed with an expression vector comprising a nucleic acid encoding a ketopantothenate reductase. The specification fails to provide additional representative species of the claimed genus of microorganisms by any identifying characteristics or properties other than the functionality of being a microorganism overexpressing a *Bacillus* or *Bacillus subtilis* pantothenate biosynthetic enzyme, a ketopantoate reductase-overexpressing microorganism, a manipulated microorganism, or a microorganism having a mutant *coaX* or pantothenate kinase and co-expressing *panE*. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

[12] Claims 1, 2, 7, 12, 19, 24, 26-28, 33, 34, 49, and 51 are rejected under 35 U.S.C. 112, first paragraph. Regarding claims 1 and 2, the specification, while being enabling for a method for increased production of pantoate and pantothenate using a microorganism transformed with an expression vector comprising SEQ ID NO:29 encoding the *Bacillus subtilis* ketopantoate reductase of SEQ ID NO:30, does not reasonably provide enablement for a method of producing *any* panto-compound by culturing a microorganism overexpressing *any Bacillus* or *Bacillus subtilis* ketopantoate reductase. Regarding claims 19, 24, and 26-28, the specification, while being enabling for a method for increased production of pantoate and pantothenate using a microorganism transformed with an expression vector comprising a nucleic acid encoding an *E. coli* or *S. typhimurium* ketopantoate reductase and optionally wherein pantothenate is produced at a level of up to 2 gram/liter, does not reasonably enable a beta-alanine independent high yield production method for producing pantothenate using a microorganism overexpressing *any* manipulated microorganism, and optionally further having a deregulated pantothenate biosynthetic pathway, overexpressing *any* ketopantoate reductase, is transformed with a vector comprising *any panE* nucleic acid, or optionally produces pantothenate at the levels recited in

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claim 28. Regarding claims 33 and 34, the specification, while being enabling for a method for increased production of pantoate and pantothenate using a microorganism transformed with an expression vector comprising the nucleic acid of SEQ ID NO:29 encoding the *Bacillus subtilis* ketopantoate reductase of SEQ ID NO:30, does not reasonably enable a beta-alanine independent high yield production method for producing pantothenate using a microorganism overexpressing *any* manipulated microorganism, and optionally further having a deregulated pantothenate biosynthetic pathway, and overexpressing *any* *Bacillus* ketopantoate reductase or panE nucleic acid. Regarding claims 49 and 51, the specification while being enabling for a method for enhancing production of pantothenate using a *Bacillus* having a deletion of the coaX gene of SEQ ID NO:9, a microorganism transformed with an expression vector comprising a nucleic acid encoding an S176L mutation in SEQ ID NO:2 or a Y181H mutation in the coaA gene product of SEQ ID NO:3 and co-transformed with an expression vector comprising a nucleic acid encoding an E. coli or S. typhimurium ketopantoate reductase, does not reasonably provide enablement for a method of production of *any* panto-compound by culturing *any* mutant microorganism having *any* mutant coaX gene, culturing *any* pantothenate kinase mutant microorganism, or culturing *any* microorganism that has a deregulated pantothenate biosynthetic pathway and *any* mutation that results in reduced pantothenate kinase activity.

Undue experimentation would be required for a skilled artisan to make and use the entire scope of claimed methods. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The Factors most relevant to the instant rejection are addressed below.

- The breadth of the claims: The claims are *so* broad as to encompass methods using all of the microorganisms as described above. However, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention

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commensurate in scope with these claims. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the large number of microorganisms broadly encompassed by the claims. In this case, the disclosure is limited to a method for increased production of pantoate and pantothenate using a microorganism transformed with an expression vector comprising SEQ ID NO:29 encoding the *Bacillus subtilis* ketopantoate reductase of SEQ ID NO:30, a method for increased production of pantoate and pantothenate using a microorganism transformed with an expression vector comprising a nucleic acid encoding an E. coli or S. typhimurium ketopantoate reductase and optionally wherein pantothenate is produced at a level of up to 2 gram/liter, a method for increased production of pantoate and pantothenate using a microorganism transformed with an expression vector comprising the nucleic acid of SEQ ID NO:29 encoding the *Bacillus subtilis* ketopantoate reductase of SEQ ID NO:30, and a method for enhancing production of pantothenate using a *Bacillus* having a deletion of the *coaX* gene of SEQ ID NO:9, a microorganism transformed with an expression vector comprising a nucleic acid encoding an S176L mutation in SEQ ID NO:2 or a Y181H mutation in the *coaA* gene product of SEQ ID NO:3 and co-transformed with an expression vector comprising a nucleic acid encoding an E. coli or S. typhimurium ketopantoate reductase.

- The lack of guidance and working examples provided in the specification: Regarding claims 1 and 2, the specification provides guidance in the form of a single working example for isolation of a microorganism overexpressing a ketopantoate reductase with the ability to increase yields of pantothenate, i.e., a microorganism transformed with an expression vector comprising SEQ ID NO:29 for overexpression of the ketopantoate reductase of SEQ ID NO:30 (see Example II at pages 65-68). The specification fails to provide guidance as to isolation of other microorganisms overexpressing *Bacillus* or *Bacillus subtilis* ketopantoate reductase, including microorganisms with, e.g., altered promoters and enhancers, that would increase expression of endogenous ketopantoate reductase. Similarly with claims 7 and 12, the specification has provided guidance only for overexpressing ketopantoate reductase by transforming a microorganism with an expression vector comprising a nucleic acid encoding said ketopantoate reductase. Regarding claims 19, 24, 26-28, 33, and 34, the specification has provided

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guidance as to only a single manipulated microorganism and optionally wherein the microorganism has a deregulated pantothenate biosynthetic pathway for beta-alanine independent pantothenate production, i.e., a microorganism overexpressing ketopantoate reductase, wherein overexpression is achieved by transforming the microorganism with an expression vector comprising a nucleic acid encoding the ketopantoate reductase. Also, the specification fails to provide guidance regarding a method for the production of pantothenate at levels from 10, 20, or 40 g/L to *any* upper limit and only provides guidance for production of pantothenate at levels up to 2 g/L when using a microorganism overexpressing a ketopantoate reductase. Regarding claims 33 and 34, the specification provides guidance for isolation of only a single nucleic acid encoding a ketopantoate reductase whose overexpression results in increased pantothenate yields. Regarding claims 49 and 51, the specification provides guidance for only two mutations of the *coaX* gene encoding pantothenate kinase that result in a microorganism having the desired biological activity (see Example XV, pages 96-98 of the instant specification). Regarding claims 19, 24, 26-28, 33, 34, 49, and 51, the specification and the prior art teach the isolation of only three working examples of nucleic acids encoding ketopantoate reductases – *E. coli*, *S. typhimurium*, and the nucleic acid of SEQ ID NO:29 encoding *B. subtilis* ketopantoate reductase.

- The unpredictability of the art: Regarding all claims, one of skill in the art would recognize the high degree of unpredictability in modifying a microorganism with the expectation of obtaining the desired result – in this case overexpression of ketopantoate reductase resulting in production of a panto-compound, particularly in view of the lack of guidance provided in the specification regarding such modifications. The modifications that can be made to a microorganism or encoding nucleic acid with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is highly unpredictable. For example, Baigori et al. (*J Bacteriol* 173:4240-4242) teach mutagenesis of a *B. subtilis* strain resulting in a pantoate/pantothenate auxotroph with significantly reduced ketopantoate reductase activity (page 4240, right column, top and page 4241, Table 2). Furthermore, based on the specification, it appears that even overexpressing ketopantoate reductase using an expression vector may not predictably enhance production of a panto-compound. For example,

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the specification teaches that overexpression of panE2 results in a *decrease* in pantothenate production (see page 68, lines 13-17). Furthermore, the methods of isolating genes as described in the specification, e.g., PCR and hybridization, are structure dependent and it is highly unpredictable that a primer or probe used for the isolation of a first gene can be used for isolation of other genes as the sequences may not be sufficiently identical and no guidance has been provided of the homology of the genes in other organisms. Regarding claim 28, one of skill in the art, based on the guidance provided in the specification, would predict that such levels of pantothenate as recited in the claim could *not* be obtained. Regarding claims 49 and 51, one of skill in the art would recognize the high degree of unpredictability in mutating a *coaX* gene or a nucleic acid encoding a pantothenate kinase with an expectation of obtaining an expressed enzyme having the desired activity. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

- The amount of necessary experimentation is not routine: Due to the lack of guidance and working examples, and the high degree of unpredictability in the art as described above, one of skill in the art would recognize the amount of experimentation required to make the entire scope of claimed methods is beyond routine. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple modifications to a microorganism, nucleic acid, or polypeptide, as encompassed by the instant claims.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any . The scope of the claims must bear a

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reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[13] Claims 1, 2, 7, 19, 24, 26, 27, 33, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Baigori et al. (*J Bacteriol* 173:4240-4242). Claims 1 and 2 are drawn to a method of producing a panto-compound comprising culturing a microorganism that overexpresses at least one *Bacillus* or *Bacillus subtilis* pantothenate biosynthetic enzyme under conditions for production of the panto-compound. Claim 7 is drawn to a method of producing a panto-compound by culturing a ketopantoate reductase overexpressing microorganism under conditions such that the panto-compound is produced. Claim 19 is drawn to a beta-alanine independent high yield production method for producing pantothenate comprising culturing a manipulated microorganism such that pantothenate is produced at a high yield. As the examiner can find no specific definition of the term "beta-alanine independent...method", the term has been interpreted as meaning a method of producing pantothenate using a biosynthetic pathway that does not utilize beta-alanine as an intermediate (see for example, Figure 1, page 4241 of Baigori et al.). Claim 24 limits the microorganism of the method of claim 19 to further having a deregulated pantothenate biosynthetic pathway. It is noted that the term "deregulated" as recited in claim 24 is defined in the specification as meaning "alteration or modification of at least one gene in a microorganism that encodes an enzyme in a biosynthetic pathway, such that the level or

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activity of the biosynthetic enzyme in the microorganism is altered or modified" (see page 17, lines 13-16). Claims 26 and 27 limit the microorganism of claim 24 to overexpressing a ketopantoate reductase (claim 26) or being transformed with a vector comprising a panE1 nucleic acid sequence (claim 27). As the examiner can find no specific definition of the term "panE1" as recited in claim 27, in accordance with MPEP 2111, the term has been interpreted as meaning any nucleic acid encoding a ketopantoate reductase. Claims 33 and 34 limit the microorganism of claim 24 to overexpressing a *Bacillus* ketopantoate reductase (claim 33) or being transformed with a vector comprising a *Bacillus* panE1 nucleic acid sequence (claim 34).

Baigori et al. teach *Bacillus subtilis* strain UR1 that, when transformed with DNA from *Bacillus subtilis* strain BD170 to generate strain UR3, exhibited an increase in ketopantoate reductase activity from 6.43 U/mg to 25.37 U/mg (page 4240, right column, middle and page 4241, Table 2). While Baigori et al. do not specifically teach their method results in the increased production of pantoate or pantothenate, production of these compounds would have inherently resulted from the overexpression of ketopantoate reductase in *Bacillus subtilis* as Baigori et al. teach *Bacillus subtilis* has a pantothenate biosynthetic pathway (page 4240, right column). This anticipates claims 1, 2, 7, 19, 24, 26, 27, 33, and 34 as written.

[14] Claims 7, 19, 24, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Frodyma et al. (*J Biol Chem* 273:5572-5576). Claims 7, 19, 24, and 26 are drawn to methods of producing a panto-compound or pantothenate as described above (see item 13 above).

Frodyma et al. teach overexpression of a *Salmonella typhimurium* apbA gene encoding ketopantoate reductase in an *Escherichia coli* host cell (page 5572, right column, bottom) and overexpression of the ketopantoate reductase was induced using IPTG to induce expression of T7 polymerase. Frodyma et al. teach apbA is the locus previously designated panE (page 5572, left column, bottom) and that ketopantoate reductase has a well-described role in *S. typhimurium* and *E. coli* pantothenate biosynthesis (page 5572, right column, top). While Frodyma et al. do not specifically teach their method results in the production of pantoate and pantothenate, the production of these compounds

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would have inherently resulted from the overexpression of *apbA* in *E. coli* as Frodmya et al. teach *E. coli* has a pantothenate biosynthetic pathway (page 5572, right column, top). This anticipates claims 7, 19, 24, and 26 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

[15] Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Frodyma et al. in view of Hikichi et al. (US Patent 5,518,906). Claim 12 limits the microorganism of the method of claim 7 to further comprising at least one pantothenate biosynthetic enzyme in addition to overexpressing ketopantoate reductase.

Frodyma et al. disclose the teachings as described above (see items 13 and 14 above). Additionally, Frodyma et al. teach *panE* encoding ketopantoate reductase is a gene of the pantothenate biosynthetic pathway (see page 5573, Figure 1). Frodyma et al. do not teach or suggest overexpressing their pantothenate biosynthetic enzyme in addition to ketopantoate reductase.

Hikichi et al. teach a method for the production of pantoate and pantothenate (referred to as pantoic acid and pantothenic acid, respectively, in Hikichi et al.) using an *E. coli* host transformed with plasmid pFV31 comprising *E. coli* *panB*, *panC*, and *panD* genes encoding ketopantoate hydroxymethyltransferase, pantothenate synthase, and aspartate-alpha-decarboxylase, respectively (column 7, lines 27-31 and Examples 3 and 6). Hikichi et al. teaches pantothenate is a useful vitamin substance and that pantoate is useful as an important intermediate for synthesis of pantothenate and CoA (column 1, lines 10-12). Hikichi et al. teach that a strain transformed with a plasmid carrying genes

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involved in the biosynthesis of pantothenate accumulates increased levels of pantothenate in the culture medium (column 2, lines 34-38).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Frodyma et al. and Hikichi et al. for a method for producing pantothenate using the host cell of Frodyma et al. overexpressing ketopantoate reductase additionally overexpressing the panB, panC, and panD genes of Hikichi et al. One would have been motivated for a method for producing pantothenate using the host cell of Frodyma et al. overexpressing ketopantoate reductase additionally overexpressing the panB, panC, and panD genes of Hikichi et al. because of the teaching of Hikichi et al. who teaches a strain transformed with a plasmid carrying genes involved in the biosynthesis of pantothenate accumulates increased levels of pantothenate in the culture medium as described above. One would have a reasonable expectation of success for a method for producing pantothenate using the host cell of Frodyma et al. overexpressing ketopantoate reductase additionally overexpressing the panB, panC, and panD genes of Hikichi et al. because of the results of Frodyma et al. and Hikichi et al. Therefore, claim 12, drawn to a method for the production of a panto-compound as described above would have been obvious to one of ordinary skill in the art.

[16] Claims 49 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baigori et al. or Frodyma et al. in view of Hikichi et al. as applied to claim 12 above, and further in view of Vallari et al. (*J Bacteriol* 170:3961-3966) and Leung (Coenzyme-A Technologies Inc., Technical Articles and Scientific Research, "Coenzyme-A 'The Master Coenzyme'"). Claim 49 is drawn to a method for enhancing production of a panto-compound by culturing a microorganism having a mutant coaX gene or a mutant pantothenate kinase and further overexpresses panE under conditions such that the panto-compound is produced. As the examiner can find no specific definition of the term "coaX" as recited in claim 49, in accordance with MPEP 2111, the term has been interpreted as meaning any nucleic acid encoding a pantothenate kinase. Claim 51 is drawn to a method for enhancing production of a panto-compound by culturing a microorganism that has a deregulated pantothenate biosynthetic pathway and a mutation

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resulting in reduced pantothenate kinase activity under conditions such that the panto-compound is produced.

Frodyma et al. and Hikichi et al. disclose the teachings as described above (see items 13-15 above). as stated above Hikichi et al. teach pantoate is useful as an important intermediate for synthesis of pantothenate and CoA (column 1, lines 10-12). The references of Frodyma et al. and Hikichi et al. do not combine to teach or suggest a microorganism comprising a mutant *coaX* or a mutant pantothenate kinase or the use thereof for producing a panto-compound.

Vallari et al. teach the regulation of pantothenate kinase appears to be the most important determinant of the CoA biosynthetic rate and that pantothenate kinase is feedback regulated by CoA (page 3961, left column). Vallari et al. teach an *E. coli* strain, DV79, expressing a feedback resistant pantothenate kinase that has 29 % kinase activity of the wild type (page 3963, left column). Vallari et al. teach this strain had CoA levels that were significantly elevated relative to strains expressing wild type pantothenate kinase (page 3961, abstract).

Also, at the time of the invention, it was known in the art that CoA was used as a nutritional supplement. For example, Leung (Coenzyme-A Technologies Inc., Technical Articles and Scientific Research, "Coenzyme-A 'The Master Coenzyme'") extol the beneficial effects of pantothenic acid and CoA in treating acne.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Frodyma et al., Hikichi et al., Vallari et al., and Leung for a method for producing CoA using the host cell of Vallari et al. expressing the mutant pantothenate kinase and additionally co-expressing the ketopantoate reductase of Frodyma et al. and the *panB*, *panC*, and *panD* genes of Hikichi et al. One would have been motivated for a method for producing CoA using the mutant pantothenate kinase and additionally co-expressing the ketopantoate reductase of Frodyma et al. and the *panB*, *panC*, and *panD* genes of Hikichi et al. because of the teaching of Hikichi et al. who teaches a strain transformed with a plasmid carrying genes involved in the biosynthesis of pantothenate accumulates increased levels of pantothenate in the culture medium and that pantoate is useful as an

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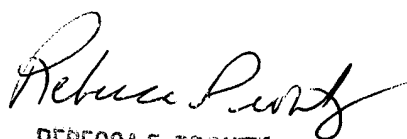
important intermediate for synthesis of CoA (column 1, lines 10-12), Vallari et al. who teach CoA is an essential cofactor in numerous metabolic pathways, and Leung who teach the beneficial effects of CoA supplementation. One would have a reasonable expectation of success for a method for producing pantothenate using a method for producing CoA using the host cell of Vallari et al. expressing the mutant pantothenate kinase and additionally co-expressing the ketopentolate reductase of Frodyma et al. and the panB, panC, and panD genes of Hikichi et al. because of the results of Frodyma et al., Hikichi et al., and Vallari et al. Therefore, claims 49 and 51, drawn to methods for the production of a panto-compound as described above would have been obvious to one of ordinary skill in the art.

Conclusion

[17] All claims are rejected. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for official papers filed to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652


REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600
1600